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ORIGINAL ARTICLE

Prescribed Water Intake in Autosomal Dominant Polycystic Kidney Disease

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Abstract

BACKGROUND Arginine vasopressin promotes kidney cyst growth in autosomal dominant polycystic kidney disease (ADPKD). Increased water intake reduces arginine vasopressin and urine osmolality and may slow kidney cyst growth.

METHODS In this randomized controlled 3-year clinical trial, we randomly assigned adults with ADPKD who had a height-corrected total kidney volume in Mayo imaging subclass categories 1B to 1E and an estimated glomerular filtration rate of 30 ml/min/1.73 m^2 or greater to (1) water intake prescribed to reduce 24-hour urine osmolality to 270 mOsmol/kg or less or (2) ad libitum water intake irrespective of 24-hour urine osmolality. The primary end point was the percentage annualized rate of change in height-corrected total kidney volume.

RESULTS A total of 184 patients participated in either the ad libitum water intake group (n=92) or the prescribed water intake group (n=92). Over 3 years, there was no difference in the annualized rate of change in height-corrected total kidney volume between the ad libitum (7.8% per year; 95% confidence interval [CI], 6.6 to 9.0) and prescribed (6.8% per year; 95% CI, 5.8 to 7.7) water intake groups (mean difference, −0.97% per year; 95% CI, −2.37 to 0.44; P=0.18). The difference in mean 24-hour urine osmolality between the ad libitum and prescribed water intake groups was −91 mOsmol/kg (95% CI, −127 to −54 mOsmol/kg), with 52.3% of patients achieving adherence to the target 24-hour urine osmolality and no reduction in serum copeptin over 3 years. The frequency of adverse events was similar between groups.

CONCLUSIONS For patients with ADPKD, prescribed water intake was not associated with excess adverse events and achieved the target 24-hour urine osmolality for half of

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the patients but did not reduce copeptin or slow the growth of total kidney volume over 3 years compared with ad libitum water intake. (Funded by the National Health and Medical Research Council of Australia [grant GNT1138533], Danone Research, PKD Australia, the University of Sydney, and the Westmead Medical Research Foundation; Australian New Zealand Clinical Trials Registry number, ACTRN12614001216606).

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease and is due to heterozygous germline variants in either *PKD1* or *PKD2*.[1] In young adults, the phenotype of ADPKD is characterized by multiple small subcentimeter kidney cysts that slowly expand, causing chronic kidney pain and kidney failure by mid-life due to massive kidney enlargement.[2] Over the last decade, high-quality evidence from randomized controlled trials indicates that arginine vasopressin is a critical growth factor for kidney cysts and a target for therapeutic intervention in ADPKD.[3–9]

Increasing water intake to maintain adequate hydration reduces arginine vasopressin and has been suggested as a simple approach to slow the growth of kidney cysts, given that water is readily accessible and most people would agree that it is not associated with toxicity within reasonable consumption limits.[10–13] However, findings in preclinical models of cystic kidney disease have been inconsistent,[12,14,15] and previous clinical trials in humans were uncontrolled or of short duration (1 to 52 weeks).[16–20] The absence of evidence for increased water intake in the treatment of ADPKD has led to uncertainty in clinical practice, and a long-term randomized controlled clinical trial with disease-specific end points has been a high priority for both patients and clinicians.[12,21–23]

We performed a randomized controlled trial to test the hypothesis that prescribing increased water intake to a degree to lower urine osmolality to iso-osmolar levels over 3 years would reduce kidney cyst growth in patients with ADPKD. To evaluate this hypothesis, we used the validated method by Wang et al.[16] to prescribe and personalize the amount of water required to suppress urine osmolality. Furthermore, based on a systematic review of methods to increase water intake,[24] a multipronged approach, including coaching and self-monitoring tools, was used to implement the study intervention.

Methods

TRIAL DESIGN AND OVERSIGHT

PREVENT-ADPKD (the Randomised Controlled Trial to Determine the Efficacy and Safety of Prescribed Water Intake to Prevent Kidney Failure Due to Autosomal Dominant Polycystic Kidney Disease) was an investigator-initiated, 3-year randomized controlled trial conducted at 13 centers in Australia from December 2015 to June 2021. The study protocol was published previously (Supplementary Appendix contains additional details on the methods and results, along with all supplementary figures and tables; the original and final protocols and statistical analysis plans, along with a table of amendments, can be found with the full text of this article in Supplementary Protocol at evidence.nejm.org;)[25] and was approved by the human research ethics committees at all study sites. The major funders of the trial were the National Health and Medical Research Council of Australia and Danone Research, and neither had any decisional role in the trial design, data collection, data analysis, data interpretation, or the writing of the manuscript. The trial was undertaken by a mobile study team who visited all sites to undertake study procedures except during the Covid-19 pandemic (see the "Trial Procedures"). The trial steering committee consisted of the authors who designed and oversaw the trial. An independent data safety monitoring board reviewed data quality and evidence for treatment harm.

INCLUSION AND EXCLUSION CRITERIA

Adults were eligible to participate in the PREVENT-ADPKD trial if they were between 18 and 67 years of age with a diagnosis of ADPKD, had an estimated glomerular filtration rate (eGFR) of 30 ml/min/1.73 m^2 or greater, had a height-corrected total kidney volume in Mayo imaging subclass categories 1B to 1E, and provided written informed consent.[25,26] The key exclusion criteria were the presence of potential safety risks for increased water intake, a contraindication to undergoing magnetic resonance imaging (MRI), a subjective risk of noncompliance with study procedures as determined by the lead

investigator, the presence of concomitant conditions that may have confounded end-point measures, and/or participation in other clinical trials (see the Supplementary Methods, page 4, in Supplementary Appendix and the final study protocol, page 146, in Supplementary Protocol).[27] In addition, due to the risk of exacerbating hyponatremia, diuretics were withdrawn completely, in consultation with the treating nephrologist, if patients met the eligibility criteria and were willing to proceed.

TRIAL PROCEDURES

After the screening visit, a baseline kidney MRI scan, eGFR measurement, and two 24-hour urine collections for osmolality were performed during a run-in period of up to 16 weeks. Eligible patients were randomly assigned 1:1 to either the ad libitum water intake group or the prescribed water intake group, stratified by baseline eGFR (less than 60 or 60 ml/min/1.73 m^2 or greater). Randomization was performed centrally with a secure Web-based server in variable permuted blocks of four using a validated list provided by the trial statistician. At the second study visit, patients allocated to the ad libitum water intake group were advised to continue with their usual water intake and treatment. A study dietitian reviewed the health records for patients allocated to the prescribed water intake group and calculated an individualized water prescription using the free water clearance formula, as described by Wang et al.[16] This formula was designed to determine the amount of water intake required to reduce urine osmolality to 270 mOsmol/kg or less using the mean baseline 24-hour urine osmolality.[16] The study dietitian provided personalized counseling for consuming the water prescription, considering the patient's lifestyle, dietary solute intake, and preferences. In addition, patients self-monitored urine-specific gravity (daily for the first 2 weeks, twice weekly for the first 6 months, and then as needed) to keep it below 1.010. The water prescription was recalculated during follow-up visits using 24-hour urine osmolality (3-monthly during the first year and then 6-monthly in the second and third years). Both groups of patients underwent the same follow-up tests and visits.

On January 1, 2019, tolvaptan (a selective, competitive vasopressin 2 receptor antagonist) became available for reimbursement and part of the standard treatment for patients with ADPKD with an eGFR between 30 and 89 ml/min/1.73 m^2 together with historical evidence of a rapid decline (either greater than or equal to 5 ml/min/1.73 m^2 within 1 year or an average decline of greater than or equal to 2.5 ml/min/1.73 m^2 per year over a 5 year period). The manufacturer commenced a product familiarization program on August 20, 2018; at this time, all patients in this study were reconsented and informed that tolvaptan was available for the treatment of ADPKD and instructed to contact their treating nephrologist to determine their eligibility for treatment. If tolvaptan was commenced, an early MRI scan was performed, the prescribed water intake intervention was withdrawn (if allocated to this group), and all other follow-up visits and procedures continued (see Appendix 7 of the final study protocol in Supplementary Protocol, page 246). Furthermore, due to the Covid-19 pandemic, all visits were conducted by telehealth, and blood and urine collections were not performed between March and June 2020. Also, due to state border restrictions, all Perth and Brisbane study visits between March 2020 and June 2021 were conducted using telehealth and by local study staff who performed study procedures. No primary outcome measurements were missed.

OUTCOMES

The primary end point was the annualized rate of change (slope) in height-corrected total kidney volume (total kidney volume of both kidneys corrected for height) from baseline to the month 18 and month 36 time points, normalized as a percentage, as described previously.[27] Imaging acquisition was standardized using a set sequence protocol and method at all imaging sites. To assess total kidney volume, left and right kidney MRI-estimated volumes were quantified by blinded study personnel. Deidentified kidney images identified by MRI were encrypted and analyzed by the Imaging Core of the Mayo Translational PKD Center (Rochester, MN).

The secondary end points were as follows: surrogate markers of systemic arginine vasopressin activity (24-hour urine osmolality and volume and serum copeptin), kidney disease progression (slope of decline in eGFR from baseline and 3 months to 36 months,[28] mean arterial pressure, and spot urine albumin-to-creatinine ratio), kidney pain using a clinical outcome scale,[25] a composite end point of kidney disease progression as described previously (defined as a 25% or greater reduction in eGFR from baseline or week 12, worsening hypertension, worsening albuminuria, and clinically significant kidney pain) (see the Supplementary Methods, pages 9 and 10, in Supplementary Appendix),[29] a physiological measure of treatment adherence

(the percentage of patients with 24-hour urine osmolality less than 300 mOsmol/kg at each time point and the percentage of patients with 24-hour urine osmolality less than 300 mOsmol/kg for more than 50% of the time points), and treatment acceptability (the number of patients reporting that water intake can be maintained lifelong and the number of participants withdrawing from the study). Safety and tolerability were assessed by clinical review of all adverse events (AEs), including those of special interest (hyponatremia defined as a serum sodium of 134 mmol/l or less and ADPKD-related medical events).

STATISTICAL ANALYSIS

The sample size was determined assuming an annual rate of increase in height-corrected total kidney volume of a mean (±SD) 5.5±3.8% per year based on previous cohort studies on ADPKD.[30] An enrollment of 180 patients (n=90 per arm) was predicted to have 87% power to detect a difference of 1.9 percentage points per year in height-corrected total kidney volume using a two-sided test and a 0.05 level of significance, based on a dropout rate of 15%. The primary end point (annualized rate of change of height-corrected total kidney volume) was analyzed using a linear mixed-effects model with log10 height-corrected total kidney volume of the baseline, month 18, and month 36 MRI scans as the end points. Time was treated as a continuous variable using the date that the MRI scans were performed. The linear mixed-effects model was fitted to the log10-transformed height-corrected total kidney volume, which included the fixed effects of baseline Mayo imaging subclasses 1B to 1E, baseline eGFR stratification category (less than 60 or 60 ml/min/1.73 m^2 or greater), mean baseline 24-hour urine osmolality (less than 400 or 400 mOsmol/kg or greater), treatment, time (as a continuous variable), and the treatment × time interaction and included the random intercept and slope. When the height-corrected total kidney volume value was missing at the month 18 or month 36 time points, the data were imputed under the missing at random assumption using multiple imputations with 100 resamples drawn. For secondary end-point analysis, no imputation was performed, and data were analyzed using a mixed model with repeated measurements. An unstructured variance-covariance matrix was used. Least squares means, least squares mean treatment differences, and their associated 95% confidence intervals (CIs) were calculated. For each secondary end point, least squares means were estimated from a mixed model with repeated measurements over the entire study period. The arithmetic difference between the least squares means for each group was then determined. All statistical analyses were performed in the intention-to-treat sample with SAS software, version 9.4.

Results

PARTICIPANT ENROLLMENT AND BASELINE CHARACTERISTICS

From December 2015 until June 2017, 1571 patients were screened for eligibility; 276 consented and attended the first study visit for screening (Fig. 1). Following screening, 187 patients (100% of recruitment target) met the eligibility criteria; 3 patients did not attend the randomization visit, and the remaining 184 were randomly assigned to the water ad libitum group (n=92) or prescribed water intake group (n=92) (Fig. 1). Overall, 85.9% of patients (158 of 184) completed the 3-year follow-up, consisting of 88.0% in the ad libitum water intake group and 83.7% in the prescribed water intake group. All patients (N=184) were included in the analysis of the primary and secondary end points. The demographic, clinical, and laboratory characteristics were balanced between the groups (Table 1 and Table S1). The mean (±SD) 24-hour urine osmolality and the median 24-hour urine volume of the total cohort at baseline were 423±165 mOsmol/kg and 2253 ml (interquartile range, 1788 to 3093 ml), respectively.

PHYSIOLOGICAL MEASURES OF TREATMENT ADHERENCE

Over 3 years, the mean 24-hour urine osmolality was 419 mOsmol/kg in the ad libitum group and 328 mOsmol/kg for the prescribed water intake group, with a treatment difference of −91 mOsmol/kg (95% CI, −127 to −54) (Fig. 2A and Table S2). Similarly, the mean 24-hour urine volumes over 3 years were 2364 ml for the ad libitum water intake group and 2997 ml for the prescribed water intake group, with a difference of 633 ml (95% CI, 369 to 896) (Fig. 2B and Table S3). The percentage of patients who met the treatment adherence criteria for 24-hour urine osmolality was 52.3% and 17.4% in the prescribed and ad libitum water intake groups, respectively (Table S4). Moreover, over the 3 years, there was no difference in the measured serum copeptin concentration between the prescribed water intake group compared with the ad libitum water intake group (mean difference, −2.0 pmol/l; 95% CI, −4.6 to 0.6) (Table S5).

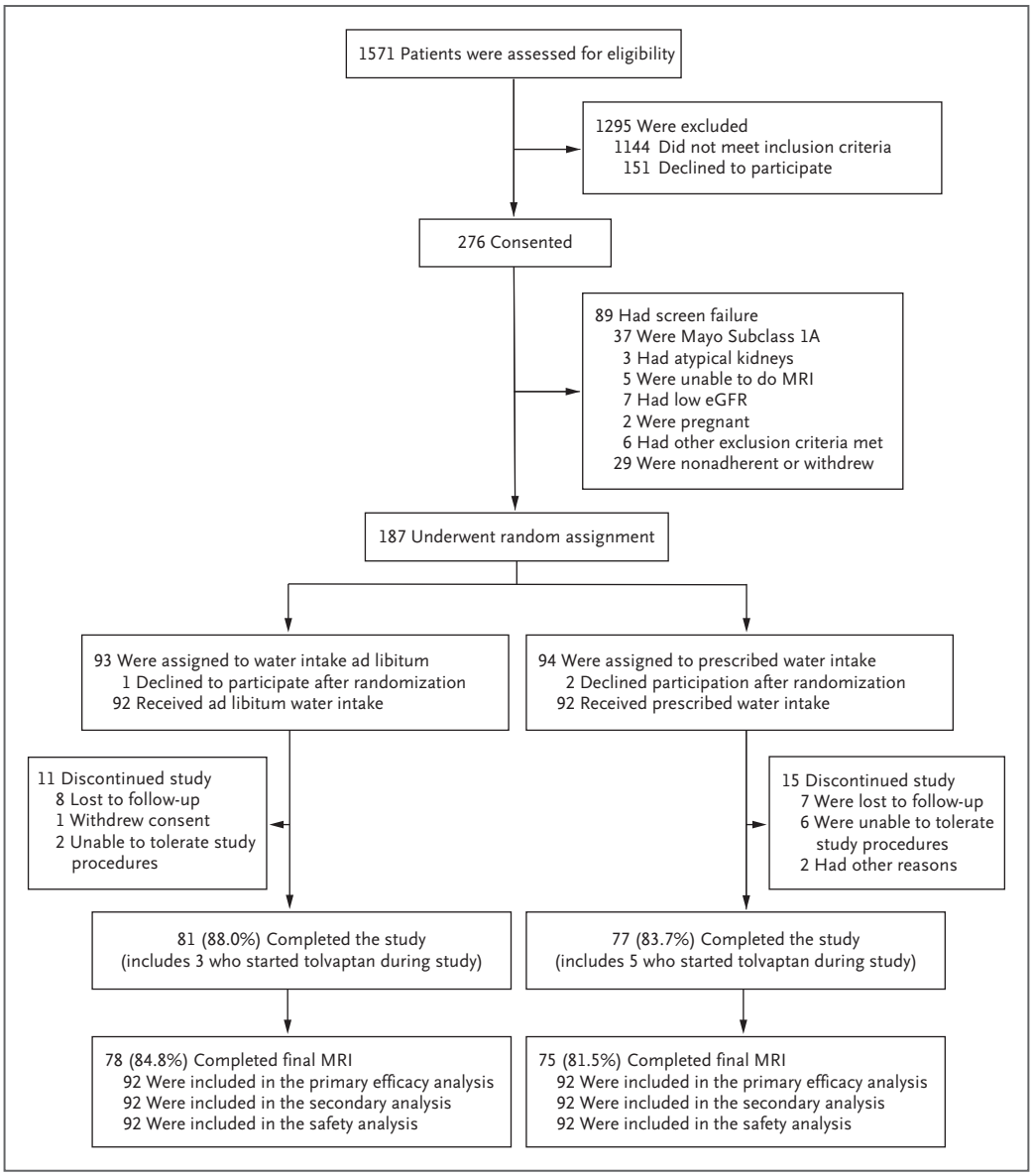

Figure 1. Patient Enrollment and Outcomes.

A total of 1571 patients were screened, of whom 187 were randomly assigned to either continue ad libitum water intake (n=94) or prescribed water intake (n=93). Three patients declined participation after randomization, leaving 92 patients in each group. Overall, 158 patients (85.9%) completed the 3-year trial, including 8 patients who commenced tolvaptan during the study period (n=3 and 5 in the ad libitum and prescribed water intake groups, respectively). All 184 patients (100%) were included in the key primary efficacy analysis, secondary analysis, and safety analysis. eGFR denotes estimated glomerular filtration rate and MRI magnetic resonance imaging.

PRIMARY END POINT

Over the 3-year period, the median absolute changes in height-corrected total kidney volume per year were 55.0 ml/m (interquartile range, 30.6 to 100.4 ml/m) in the ad libitum water intake group and 39.0 ml/m (interquartile range, 19.2 to 77.0 ml/m) in the prescribed water intake group. The annualized rate of change in height-corrected total kidney volume (percentage points of baseline kidney volume per year) was 7.8 percentage points per year (95% CI, 6.6 to 9.0) in the ad libitum water intake group versus 6.8 percentage points per year in the prescribed water intake group (95% CI, 5.8 to 7.7). There was

Table 1. Demographic, Clinical, and Laboratory Characteristics of the Patients at Baseline*		
Characteristic	**Ad Libitum Water Intake (n=92)**	**Prescribed Water Intake (n=92)**
Age — yr	42.8±11.2	43.4±10.9
Female sex — no. of patients (%)	44 (47.8)	50 (54.3)
Race or ethnicity — no. of patients (%)†		
Caucasian	69 (75.0)	65 (70.7)
Asian	12 (13.0)	14 (15.2)
Other	11 (12.0)	12 (14.2)
Medical PKD history — no. of patients (%)		
Total with any medical PKD history‡	90 (97.8)	91 (98.9)
Hypertension	72 (78.3)	67 (72.8)
Hematuria	37 (40.2)	36 (39.1)
Flank pain	50 (54.3)	37 (40.2)
Renal pain	49 (53.3)	35 (38.0)
Urinary tract infection	34 (37.0)	39 (42.4)
Nephrolithiasis	20 (21)	13 (14.1)
Kidney cyst rupture	27 (29.3)	31 (33.7)
Cardiac/vascular disease	7 (7.6)	14 (15.2)
Mean BMI — kg/m^2	27.5±5.1	26.6±4.6
Mean blood pressure — mm Hg		
Systolic	131±13	130±12
Diastolic	83±11	80±10
Current antihypertensive medications — no. of patients (%)		
Total with any antihypertensive drug treatment	68 (73.9)	64 (69.5)
Angiotensin-converting enzyme inhibitor	35 (38.0)	30 (32.6)
Angiotensin receptor blocker	30 (32.6)	33 (35.9)
Median Ht-TKV — ml/m	700.5 (485.0–1090.0)	629.0 (436.5–1124.0)
Mean eGFR — $ml/min/1.73\ m^2$§	77.8±25.3	77.7±24.8
Median 24-hour urine volume — ml	2280 (1924–2998)	2228 (1548–3100)
Mean 24-hour urine osmolality — mOsmol/kg	416±147	429±181
Median plasma copeptin — pmol/l	6.5 (3.8–12.4)	5.9 (3.1–13.0)

* Values are presented as the mean (±SD) or median (interquartile range) unless indicated otherwise. An expanded version of this table is presented as Table S1. BMI denotes body mass index, eGFR estimated glomerular filtration rate, Ht-TKV height-corrected total kidney volume, IQR interquartile range, and PKD polycystic kidney disease.

† Race was self-reported.

‡ Denotes the total number of patients with a history of medical events reasonably attributable to PKD.

§ The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

no difference in the rate of growth between the prescribed and ad libitum water intake groups (−0.97 percentage points per year; 95% CI, −2.37 to 0.44; P=0.18) (Fig. 3A and Table S6). Eight patients started tolvaptan during the study period (n=5 and 3 in the prescribed and ad libitum water intake groups, respectively; Table S7). While receiving the intervention and before any doses of tolvaptan were taken, the annualized rate of change in height-corrected total kidney volume was 7.8 percentage points per year in the ad libitum water intake group and 6.6 percentage points per year in the prescribed water intake group, with a relative change in the rate of growth for the prescribed versus ad libitum water intake groups of −1.11 (95% CI, −2.5 to 0.3; P=0.13) (Table S8). Similarly, sensitivity analysis using observed data or control-based multiple imputation showed that there were no differences in the annualized rate of change in height-corrected total kidney volume between the groups (Tables S9 and S10). Furthermore, there was no relationship between mean 24-hour urine osmolality and the annual change in height-corrected total kidney volume in a locally weighted scatterplot smoothing analysis (Fig. S1).

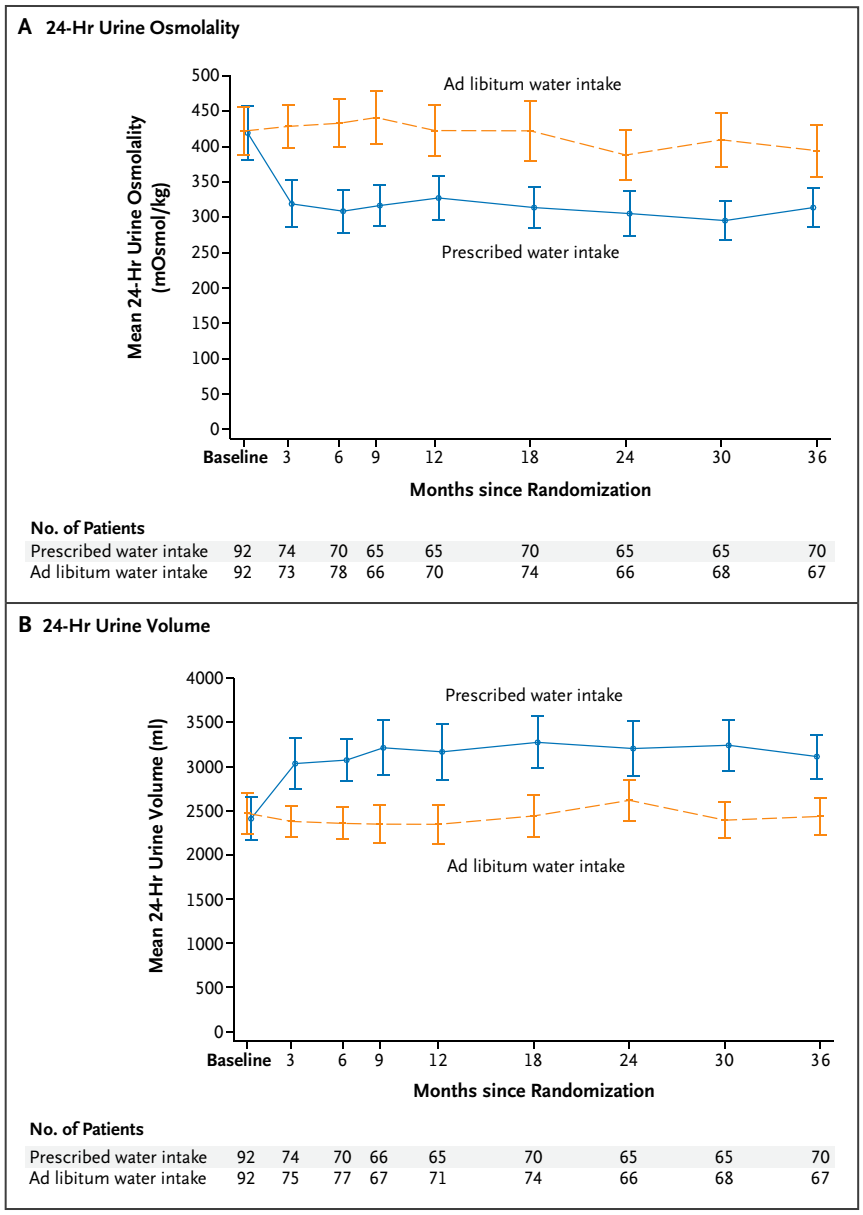

Figure 2. Effect of Prescribed Water Intake on 24-Hour Urine Osmolality and Volume.

Changes in 24-hour urine osmolality (A) and 24-hour urine volume (B) in the prescribed water intake and ad libitum water intake groups over the 3 years are shown. Individual data points indicate mean values of patients from the two groups, and error bars indicate 95% confidence intervals.

SECONDARY END POINTS

Slope of Kidney Function Change

There was no difference in the annual decline in eGFR from pretreatment (baseline) through 3 years for the ad libitum (−2.38 ml/min/1.73 m^2 per year; 95% CI, −3.13 to −1.63) and prescribed (−2.31 ml/min/1.73 m^2 per year; 95% CI, −3.07 to −1.55) water intake groups, with a mean difference of 0.07 ml/min/1.73 m^2 per year (95% CI, −1.00 to 1.14) (Fig. 3B and Table S11). Similarly, there was no difference in the annual decline in eGFR from posttreatment (week 12) through 3 years (Tables S12–S14).

Other Secondary End Points

The hazard ratio of the composite end point of investigator-assessed clinical events of ADPKD progression (as described

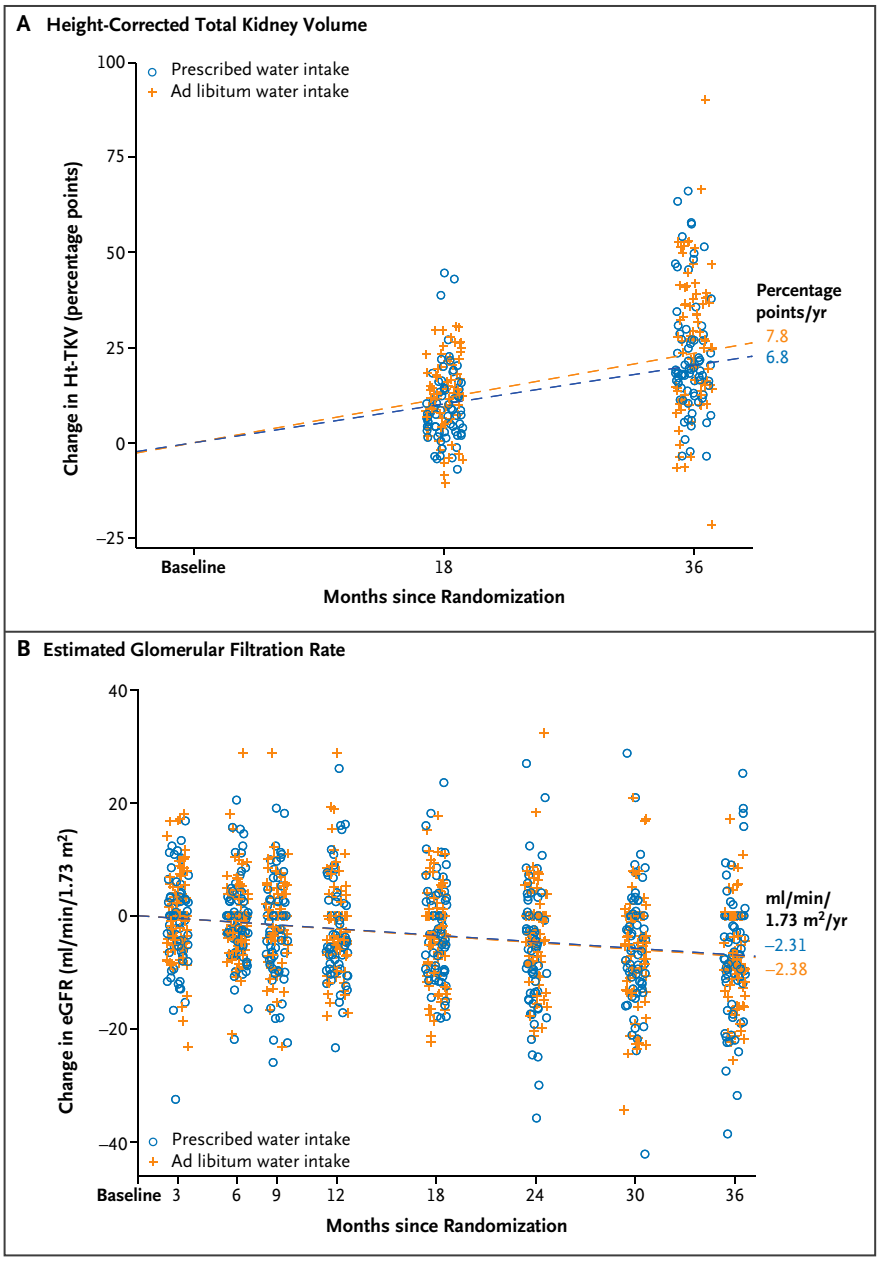

Figure 3. Effect of Prescribed Water Intake on the Annualized Rate of Change in the Height-Corrected Total Kidney Volume and the Estimated Glomerular Filtration Rate.

(A) The slopes of the estimated rate of growth in height-corrected total kidney volume (Ht-TKV) in the intention-to-treat population over the 3 years are shown, with individual data points depicted as blue circles or orange crosses (for patients in the prescribed or ad libitum water intake groups, respectively). The slope was calculated using the Ht-TKV calculated at baseline and months 18 and 36 postrandomization. The estimated annualized change in Ht-TKV was 7.8 percentage points in the ad libitum water intake group and 6.8 percentage points in the prescribed water intake group. (B) The slopes of the change in estimated glomerular filtration rate (eGFR) over the 3 years are also shown, with individual data points depicted as blue circles or orange crosses (for patients in the prescribed or ad libitum water intake groups, respectively). The rate of annual decline (baseline through 3 years) was −2.38 ml/min/1.73 m^2 per year in the ad libitum water intake group and −2.31 ml/min/1.73 m^2 per year in the prescribed water intake group. The eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration formula using serum creatinine readings from all visits, baseline (week 0), and up to month 36 postrandomization.

earlier) in the prescribed water intake group was not different from the ad libitum group (hazard ratio, 0.91; 95% CI, 0.73 to 1.13). In addition, over the 3 years, there was no difference between the groups for the other secondary end points (Tables S15–S21). Furthermore, the proportion of patients stating that the prescribed water intake intervention could not be maintained lifelong increased from 8.8% at week 26 to 20.8% at week 156 (Table S22).

ADVERSE EVENTS

Eight patients in the prescribed water intake group and two patients in the ad libitum water intake group developed hyponatremia (total of 10 episodes) (Table 2 and Table S23). Nine episodes were mild, one was moderate, and all cases resolved except for a single patient in the ad libitum water intake group who developed intermittent hyponatremia during the study period that persisted until the final study visit (Table 2). Overall, the proportion of patients experiencing AEs was similar in the two groups (Table 2 and Tables S24–S27).

Table 2. Number of Patients Who Experienced at Least One Adverse Event of Special Interest by Group*

Adverse Event	Ad Libitum Water Intake (n=92)	Prescribed Water Intake (n=92)
Hyponatremia		
All episodes	2	8
Categorized by severity — mmol/l		
Mild (130–135)	2†	7
Moderate (125–129)	0	1
Severe (<125)	0	0
Kidney complications		
Macrohematuria	8	14
Nephrolithiasis	6	2
Urinary tract infection	12	14
Dysuria	7	6
Kidney cyst infection	1	0
Kidney cyst rupture	2	5
>25% decline in eGFR from baseline	6	8
Doubling of serum creatinine from baseline	3	4
End-stage kidney failure	2	2
Pain‡	64	63
Cardiovascular complications		
Hypertension	43	36
Cardiovascular disorders§	12	16
Systemic complications		
Polycystic liver disease	8	6
Extrarenal cysts	17	8
Abdominal hernia	3	1
Colonic diverticula	3	0
Intracranial aneurysm	0	0

* An adverse event is any untoward medical occurrence, unfavorable and unintended signs, symptoms, or disease in the patient temporarily associated with the clinical study whether or not it was considered related to the procedures. Adverse events were documented from the time of randomization until the final visit. Adverse events of special interest were defined by the authors and include hyponatremia and PKD-related medical events (as described in the statistical analysis plan in Supplementary Protocol). eGFR denotes estimated glomerular filtration rate.

† One patient in the ad libitum water intake group had intermittent mild hyponatremia during the study period, and this persisted at month 37 and was thus considered ongoing. All other episodes of hyponatremia (including moderate hyponatremia) were resolved.

‡ Pain includes any adverse event subjectively described as abdominal, flank, back, kidney, groin, or liver.

§ Cardiovascular disorders include aortic dilatation, stenosis, atherosclerosis, deep vein thrombosis, hypotension, peripheral coldness, arrythmia, coronary artery disease, systole, heart failure, palpitations, pericarditis, valve issues, and valve incompetence.

Discussion

For patients with ADPKD and an increased risk of disease progression with a median baseline urine volume of 2.3 liters per day, prescribed water intake did not slow total kidney growth, as measured by serial MRI scans, compared with ad libitum water intake over a 3-year follow-up period, despite a consistent separation in 24-hour urine volume and urine osmolality between groups. Furthermore, differences were not observed between the groups in the prespecified secondary end points.

To our knowledge, this is one of the largest long-term, multicenter, randomized controlled trials on the effect of prescribed water intake on kidney disease progression. Previous studies on ADPKD were of short duration, were nonrandomized, and did not include a validated disease-specific primary outcome measure. Remarkably, the intervention group in our study achieved a mean 0.6-liter increase in urine volume and a mean 91 mOsmol/kg reduction in urine osmolality that occurred within 12 weeks and was sustained for the entire 3-year period. Other randomized controlled trials of water intake in kidney disease have shown similar efficacy, but the follow-up period has been shorter than the current study. In a 1-year study by Clark et al.[31] in chronic kidney disease (n=316 randomly assigned to the hydration group vs. 315 in the control group) and also in the 8-week study by El-Damanawi et al.[20] on ADPKD (n=21 randomized to the high water intake vs. 21 in the ad libitum group), patients were coached to increase water intake by at least 1.0 to 1.5 liters

per day but achieved a 0.6- and 0.75-liter increase in urine volume, respectively. In the latter study, the reduction in 24-hour urine osmolality in the high water intake group from baseline to week 8 was only from 51 mOsmol/kg.[20]

The intervention in the prescribed water intake group was resource intensive. It was implemented by a small team of highly skilled professional dietitians using a personalized and pragmatic counseling approach. The latter incorporated standardized education but also took into account individual factors that would impact the efficacy of prescribed water intake, such as high dietary solute intake and physical activity.[13,16,19] In addition, ongoing biofeedback of 24-hour urine volume and osmolality results to patients every 3 to 6 months was undertaken to reinforce the coaching. Finally, additional support with self-monitoring of urine-specific gravity, reducing dietary solute intake, and patient-centered goal setting, and telehealth support, including a short message service between study visits, was provided as necessary and complemented the intervention. This multipronged approach likely contributed to the engagement of patients and their consistent increase in 24-hour urine volume and reduction in urine osmolality, which occurred within 3 months and was maintained for 3 years.[24]

There are several possible reasons for the lack of efficacy of the intervention on the primary end point. First, the achieved mean 24-hour urine osmolality in the prescribed water intake group (328 mOsmol/kg) was higher than the prespecified goal of 270 mOsmol/kg, and only half of the patients (52.3%) fulfilled the secondary end point for physiological measures of treatment adherence. Furthermore, the proportion of patients reporting that prescribed water intake could be tolerated lifelong declined during the study. Collectively, these data suggest that the majority of patients in the prescribed water intake group found it difficult to continuously maintain compliance despite access to high-quality supporting resources. In this setting, the suppression of arginine vasopressin release, as verified by the measurement of the serum copeptin, was incomplete and inconsistent. In contrast, given that patients treated with a vasopressin receptor antagonist sustain drinking larger volumes of water, it is likely that thirst induced by pharmacological aquaresis is a stronger driver for increasing habitual fluid intake than behavioral modification implemented by coaching and self-monitoring.[23,32,33] Taken together, these data suggest that prescribing water intake, while associated with about a 10% incidence of resolvable hyponatremia, is difficult to maintain over the long term and insufficient for suppressing arginine vasopressin and kidney cyst growth in most patients with ADPKD.[33]

Second, the median urine volume of the cohort at baseline was 2.3 liters per day, indicating that some patients had habitual fluid intake that could be defined as "high" water consumption in the general population.[23,34] Therefore, the additional 0.6 liters of water consumed in the prescribed intake group probably did not have a significant additional impact on further suppressing arginine vasopressin release.[35,36] The results for high urine volume are consistent with measured and self-reported data in other populations with ADPKD[37] and they could be attributable to impaired urine concentrating ability in ADPKD together with behavioral patterns.[23,38] In this regard, patients in the ad libitum water intake group maintained a urine volume of 2.4 liters/day over the 3 years, and 17.4% achieved a urine osmolality lower than 300 mOsmol/kg for more than 50% of the time points. Thus, our study suggests that prescribed water intake counseling might have no additional value for patients with ADPKD.

The strengths of this study include its design, with clear treatment differences between the two groups in 24-hour urine osmolality and 24-hour urine volume, and a high retention rate during follow-up. The 3-year length of the trial and the use of disease-specific and validated surrogate biomarkers of progression provide greater certainty that the study hypothesis was addressed. Furthermore, the study was adequately powered to demonstrate a modest reduction in height-corrected total kidney volume of 1.9 percentage points per year. However, our study also had limitations. First, it was an open-label study, such that blinding of patients and research staff was not possible. Second, we intentionally did not exclude patients who were at target urine osmolality at baseline or coach the ad libitum group to reduce their intake to ensure that the intervention arm could be compared with a group resembling a real-world population. Third, changes in urine osmolality were potentially confounded by impaired concentrating ability in ADPKD and disease progression; thus, the amount of water required to suppress arginine vasopressin may have been underestimated.[39] Lastly, our study population included patients with an intermediate predicted rate of kidney cyst growth (Mayo 1B to 1C) as well as those with a rapid predicted rate (Mayo 1D to 1E), such that we cannot exclude the possibility of differential effects of the intervention within these subgroups.

In conclusion, prescribed water intake compared with ad libitum water intake in people with ADPKD, although associated with about a 10% incidence of reversible hyponatremia, that led to a sustained increase in urine volume and achieved target urine osmolality in half of the patients did not change MRI-measured kidney volume growth over 3 years. The results of our study do not support the routine use of prescribed enhanced water intake for people with ADPKD.

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Disclosures

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